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A pooled analysis of case-control studies of thyroid cancer

III. Oral contraceptives, menopausal replacement therapy and other female hormones

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Abstract

Objective: The relations between oral contraceptives (OC), hormone replacement therapy (HRT) for menopause, and other female hormone use and thyroid cancer risk was analyzed using the original data from 13 studies from North America, Asia and Europe.
Methods: Based on 2,132 cases and 3,301 controls, odds ratios (OR) and the corresponding 95% confidence intervals (CI) were obtained by conditional regression models, conditioning on study and age at diagnosis, and adjusting for age, radiation exposure and parity.
Results: Overall, 808 (38%) cases versus 1,290 (39%) controls had ever used OCs, corresponding to an OR of 1.2 (95% CI 1.0 to 1.4). There was no relation with duration of use, age at first use, or use before first birth. The OR was significantly increased for current OC users (OR = 1.5, 95% 1.0 to 2.1), but declined with increasing time since stopping (OR = 1.1 for > 10 years since stopping). The association was stronger for papillary cancers (OR = 1.6 for current users) than for other histologic types. No significant heterogeneity was observed across studies or geographic areas. Eight studies had data on HRT, for a total of 1,305 cases and 2,300 controls: 110 (8%) cases and 205 (9%) controls reported ever using HRT (OR = 0.8; 95% CI 0.6 to 1.1). The ORs were 1.6 (95% to 0.9 to 2.9) for use of fertility drugs, and 1.5 (95% CI 1.1 to 2.1) for lactation suppression treatment.
Conclusions: The studies considered in these analyses include most of the epidemiological data on the role of exogenous hormone use in the etiology of thyroid cancer, and they provide reassuring evidence on the absence of an association of practical relevance. The moderate excess risk in current OC users, if not due to increased surveillance for thyroid masses among OC users, is similar to that described for breast cancer, and would imply a role of female hormones on thyroid cancer promotion. There was no indication of increased thyroid cancer risk 10 or more years after discontinuing OC use.

Introduction

The majority of thyroid disorders are appreciably more frequent in women than in men, and in most populations thyroid cancer incidence is two to three times higher in females, suggesting that female hormones may be related to thyroid carcinogenesis [1]. Furthermore, the peak occurrence of thyroid carcinoma in women, but not in men, is during their reproductive years. Oral contraceptive use, like puberty and pregnancy, is associated with increased levels of serum thyroid stimulating hormone (TSH), total thyroxine and triiodothyronine [2].

Only scattered data, however, have been published on the potential relation between oral contraceptive (OC) use and thyroid cancer. In a study of 141 cases from Washington State [3], the odds ratio (OR) for ever users was of borderline significance (OR = 1.6). The relative risks also were above unity for ever use in a study of 78 cases less than 40 years of age conducted in Los Angeles county (OR = 2.4) [4], and one with 207 cases less than 55 years of age from Shanghai (OR = 1.2) [5]. No duration–risk relationship was observed in any of these studies. In studies from Connecticut [6] and Italy [7] an elevated thyroid cancer risk in young users of OCs was reported (ORs = 1.8 and 1.4 respectively), but no relation for middle aged women was seen. In contrast, no relationship was observed in case-control studies of women living in Hawaii [8] or Sweden [9, 10].

Data are scantier with reference to menopausal hormone replacement therapy (HRT). The ORs for ever use varied from 0.5 to 1.4 in five studies [3, 6, 8–10]. No consistent duration or other time-related risk relationships were observed.

These inconclusive findings are, at least in part, attributable to the limited number of subjects in each study. It is, therefore, important to combine the data of various epidemiological studies, in order to obtain more precise estimates. An analysis of pooled data would also allow us to better understand the effect of confounding factors and of time-dependent variables. In the present overview, based on 2,132 female thyroid cancer cases from 13 studies, we have considered these issues.

Materials and methods

A detailed description of the 13 studies considered has been given in a separate paper [11] and in the papers of the individual studies. The 13 studies represent all thyroid cancer case-control studies that included information on exogenous female hormone. These studies were identified through MEDLINE searches and published between 1980 and 1997, or through personal knowledge of participating investigators. Four studies were carried out in the USA, including studies in Los Angeles County [4], Western Washington [3], Hawaii [8]

Table 1. Descriptive statistics of oral contraceptives (OC) use by centre (cases:controls)

Study number and location	No. cases: No. controls	% of ever OC users	Median duration of use[a,b]	Median age at starting[a]	Median time since stopping[a,c]	% of users before first birth[a]
America – USA						
1. Los Angeles	292:292	72:69	33:36	21:21	5:5	13:16
2. Western Washington	185:393	56:56	–	–	2:1	–
3. Hawaii	140:328	36:44	72:48	24:23	9:8	19:20
4. Connecticut	108:208	52:50	24:36	22:22	5:7	16:20
Asia						
5. Hiroshima and Nagasaki, Japan	276:272	3:1	12:24	29:30	14:9	2:1
6. Shanghai, China	207:207	20:14	26:36	27:30	6:6	16:13
Europe – North						
7. Southeastern Sweden	149:186	52:54	–	24:22	–	–
8. Uppsala, Sweden	124:198	59:61	60:60	19:20	–	18:17
9. Northern Sweden	123:240	34:38	48:36	24:23	–	–
10. Norway, NHSS	–	–	–	–	–	–
11. Tromsø, Norway	55:136	45:44	36:48	22:20	–	22:20
Europe – South						
12. Northern Italy	291:427	16:15	24:20	23:25	5:5	7:7
13. Vaud, Switzerland	100:318	54:43	66:72	22:20	5:5	17:13
14. Athens, Greece	82:96	21:19	12:9	24:23	6:16	8:5
Total	2,132:3,301	38:39	36:41	22:22	6:6	12:12

[a] Never users excluded.
[b] Months.
[c] Years.

Table 2. Distribution[a] of thyroid cancer cases and controls according to selected indicators of oral contraceptive (OC) use, and corresponding odds ratios[b] (OR)

Variable	Cases		Controls		OR (95% CI)[c]
OC use					
Never	1324	(62)[d]	2011	(61)	1[e]
Ever	808	(38)	1290	(39)	1.2 (1.0–1.4)
χ^2 heterogeneity across studies 8.84; 12df ($p = 0.71$)					
Duration of OC use (months)					
Never used	1185	(66)	1773	(66)	1[e]
< 24	202	(11)	262	(10)	1.2 (1.0–1.5)
24–59	175	(10)	290	(11)	1.1 (0.8–1.4)
≥ 60	223	(12)	378	(14)	1.1 (0.9–1.4)
χ^2 heterogeneity across studies 6.98; 10df ($p = 0.73$)					
per 24 months					1.0 (0.9–1.0)
χ^2 heterogeneity across studies 6.28; 10df ($p = 0.79$)					
Age at starting OC use (years)					
Never used	1243	(64)	1837	(63)	1[e]
< 20	213	(11)	317	(11)	1.2 (0.9–1.6)
20–24	221	(11)	382	(13)	0.9 (0.7–1.2)
25–29	142	(7)	161	(6)	1.6 (1.2–2.1)
≥ 30	117	(6)	198	(7)	1.0 (0.7–1.4)
χ^2 heterogeneity across studies 6.65; 11df ($p = 0.83$)					
per 5 years increase					1.1 (0.9–1.3)
χ^2 heterogeneity across studies 4.15; 11df ($p = 0.97$)					
Time since last OC use (years)					
Never used	1091	(70)	1623	(71)	1[e]
Current	91	(6)	118	(5)	1.5 (1.0–2.1)
1–5	134	(9)	193	(8)	1.1 (0.8–1.5)
6–10	124	(8)	179	(8)	1.2 (0.9–1.7)
> 10	122	(8)	177	(9)	1.1 (0.8–1.4)
χ^2 heterogeneity across studies 10.03; 8df ($p = 0.27$)					
per 5 years increase					1.0 (0.8–1.1)
χ^2 heterogeneity across studies 13.26; 8df ($p = 0.10$)					
OC use before first birth (parous women only)					
Never users	1090	(76)	1602	(74)	1[e]
Only after	179	(12)	285	(13)	1.1 (0.8–1.5)
Also before	167	(12)	269	(12)	1.1 (0.9–1.4)
χ^2 heterogeneity across studies 26.85; 18df ($p = 0.08$)					

[a] Based on studies 1–9, 11–14 for ever use; 1, 3–6, 8, 9, 11–14 for duration of use; 1, 3–9, 11–14 for age at starting OC use; 1–6, 12–14 for time since stopping and 1, 3–6, 8, 11–14 for use before first birth.
[b] Estimates from logistic regression conditioned on study and age, and adjusted for history of radiation, age, parity, type of menopause and education.
[c] 95% confidence interval.
[d] The percentage is given in parenthesis.
[e] Reference category.

and Connecticut [6]. Two studies were conducted in Asia, one in Hiroshima and Nagasaki, Japan[†] and the other in Shanghai, China [5]. In the Japanese study, cases and controls were matched on A-bomb exposure and radiation dose. Of the seven European studies, four were conducted in Scandinavian countries – three in Sweden [9, 10, 12], and one in Norway [10] – and the other three were conducted in Northern Italy [7], the Swiss canton of Vaud [13] and Athens, Greece [14]. An additional study, conducted in Norway [15], did not have information on exogenous hormone use.

This analysis was restricted to the 2,132 female cases and 3,301 female controls. The distribution of the cases by histology was: papillary 80.2%, follicular 14.5%, medullary 1.8%, anaplastic 0.5%, other 1.0%, and undefined 2.0%.

[†] The data from this study have not yet been published. They were provided by Dr K. Mabuchi from the Radiation Effects Research Foundation Hiroshima, Japan.

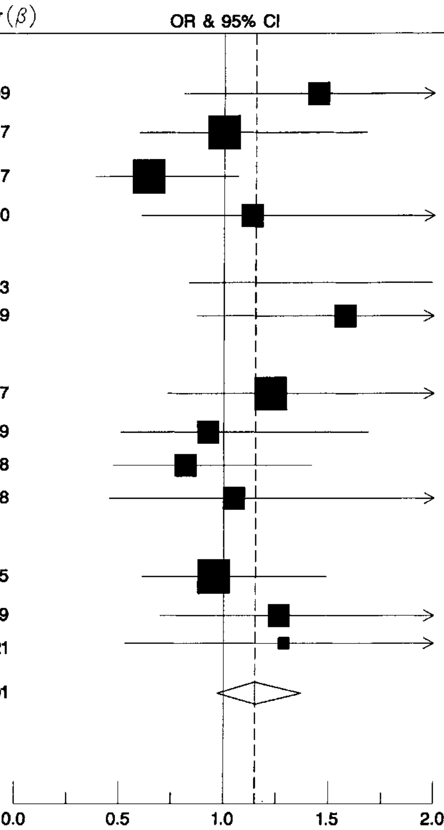
The data were all re-formatted, by the local study investigators or by the coordinating group. Information on female hormones included: ever use, total duration of use, age at first and last use for OCs and HRT, and ever use of fertility-enhancing drugs, hormones for menstrual irregularities, lactation suppression or other/undefined indications. Not all studies providing data on hormone use had complete information on time-related variables (see tables).

For each variable, a set of tables was produced describing for each study: (i) selected descriptive features of the distribution for cases and controls separately, including mean, standard deviation, quantiles, range; (ii) the frequency distribution of cases and controls according to predefined categories; (iii) the ORs and the corresponding 95% confidence intervals (CI), estimated using conditional logistic regression [16]. For matched studies, the strata were given by the matching sets, and for unmatched ones by quinquennia of age. All data were subsequently analysed together, by means of conditional logistic regression models, conditioning also on study. Heterogeneity across studies, geographical areas, study designs, and age groups was systematically tested comparing the difference in the −2 log likelihood of the models with and without interaction terms to the chi-square distribution with degrees of freedom equal to the number of interaction terms. Whenever a variable was categorical, but ordinal, the heterogeneity among trends was tested.

Since all American and Scandinavian studies had population controls, and the three South European studies used hospital controls, the heterogeneity test between geographical areas and study designs were similar, and only the former were presented. Analyses also were conducted separately for papillary and follicular cancers.

STUDY*	EVER Cases/Controls	NEVER Cases/Controls	STATISTICS β	var(β)	ODDS RATIO** OR ± SD
AMERICA – USA					
292 Los Angeles	211/202	81/90	0.37	0.09	1.5 ± 0.4
185 Western Washington	104/219	81/174	0.00	0.07	1.0 ± 0.3
140 Hawaii	51/145	89/183	−0.45	0.07	0.6 ± 0.2
109 Connecticut	56/105	52/103	0.12	0.10	1.1 ± 0.4
ASIA					
307 Japan	8/2	268/270	1.38	0.63	4.0 ± 3.2
207 China	42/28	165/179	0.45	0.09	1.6 ± 0.5
EUROPE – NORTH					
149 Southeastern Sweden	77/100	72/86	0.20	0.07	1.2 ± 0.3
133 Uppsala – Sweden	73/120	51/78	−0.08	0.09	0.9 ± 0.3
123 Northern Sweden	42/91	81/149	−0.20	0.08	0.8 ± 0.2
58 Tromsø – Norway	25/60	30/76	0.05	0.18	1.1 ± 0.4
EUROPE – SOUTH					
291 Italy	48/63	243/364	−0.05	0.05	1.0 ± 0.2
100 Switzerland	54/137	46/181	0.23	0.09	1.3 ± 0.4
82 Greece	17/18	65/78	0.25	0.21	1.3 ± 0.6
Total:	808/1290	1324/2011	0.14	0.01	1.2 ± 0.1

Test for heterogeneity between studies: χ^2 (12 d.f.) = 8.84; P = 0.71 — P = 0.1100



*Studies in each group sorted by number of cases
**Relative to never users
Adjusted for study, age, history of radiation and parity

Fig. 1. Odds ratio of thyroid cancer in ever versus never users of oral contraceptives.

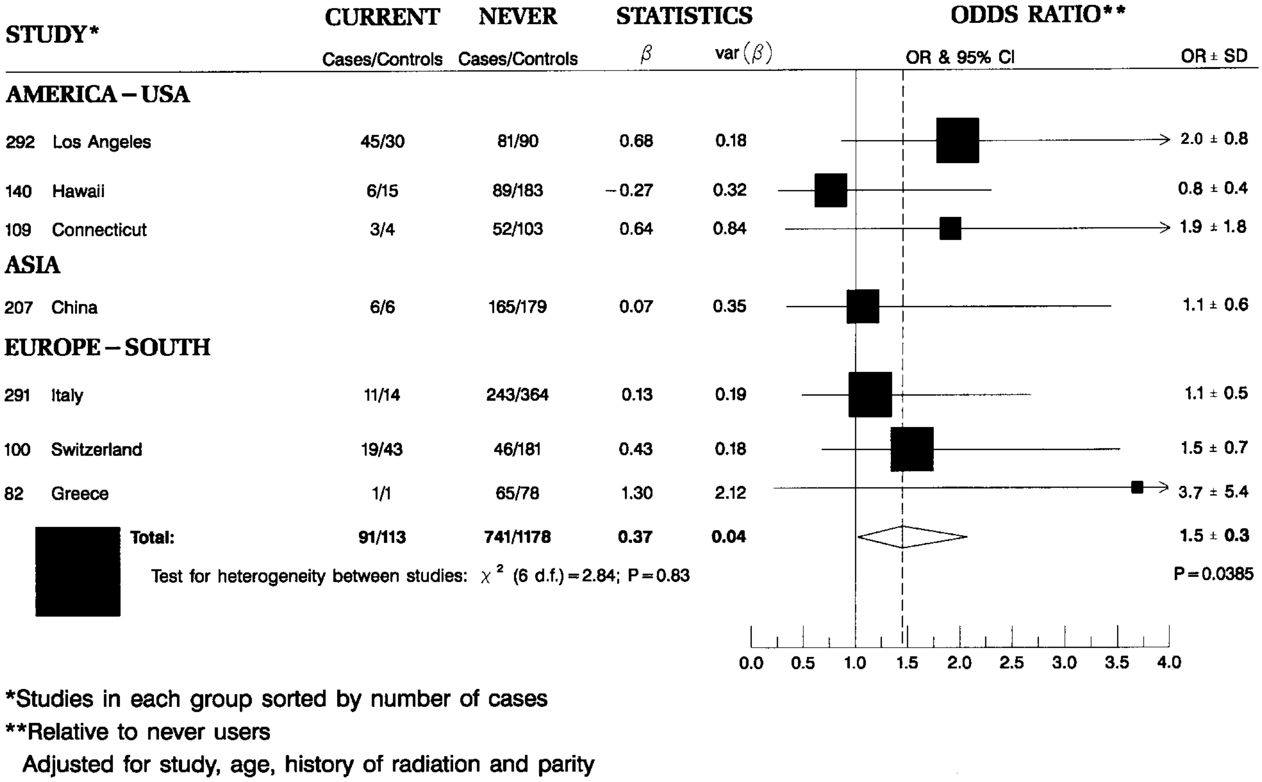


Fig. 2. Odds ratio of thyroid cancer in current versus never users of oral contraceptives.

Table 3. Odds ratios[a] of thyroid cancer according to selected indicators of oral contraceptive (OC) use in strata of geographical area and age at diagnosis

Variable	Geographical area				Age at diagnosis		
	USA	ASIA	North Europe	South Europe	≤ 35	36–55	≥ 56
OC use							
Never	1[b]	1[b]	1[b]	1[b]	1[b]	1[b]	1[b]
Ever	1.11	1.90	1.03	1.10	1.39	1.04	0.73
χ^2 heterogeneity			3.99; 3df ($p = 0.26$)			5.98; 2df ($p = 0.05$)	
Duration of OC use							
per 24 months	1.00	1.04	0.93	1.03	1.04	0.99	0.67
χ^2 heterogeneity			2.42; 3df ($p = 0.49$)			8.25; 2df ($p = 0.02$)	
Age at first OC use							
per 5 year increase	1.13	2.71	1.46	0.99	1.03	1.16	3.89
χ^2 heterogeneity			1.87; 3df ($p = 0.60$)			8.23; 2df ($p = 0.02$)	
Time since last OC use							
per 5 year increase	0.91	1.24	–	0.95	1.03	0.93	1.30
χ^2 heterogeneity			1.56; 2df ($p = 0.46$)			0.30; 2df ($p = 0.86$)	

[a] Estimates from logistic regression conditioned on center and age, and adjusted for history of radiation, age, parity, type of menopause and education.
[b] Reference category.

Results

The pattern of OC use in various studies is shown in Table 1. There was an appreciable variation in the proportion of ever users, ranging from over 50% in North America and Northern Europe, to 15–40% in Southern Europe, and only 2% in Japan. Median duration of use was longer, and median age at first

Table 4. Descriptive statistics of hormonal replacement therapy (HRT) use in postmenopausal women by centre and of use of female hormones for other indications (cases:controls)

Study number and location	% of ever HRT users	Median duration of use[a,b]	Median age at starting[a]	Median time since stopping[a,c]	% of users of drugs for	
					Infertility	Lactation suppression[d]
America – USA						
1. Los Angeles	36:48	46:14	32:40	1:7	1:2	64:56
2. Western Washington	8:4	–	42:42	6:5	–	48:35
3. Hawaii	25:34	36:84	44:44	2:5	8:3	–
4. Connecticut	19:29	48:30	46:45	7:6	2:2	58:59
Asia						
5. Hiroshima and Nagasaki, Japan	–	–	–	–	–	2:1
6. Shanghai, China	–	–	–	–	–	–
Europe – North						
7. Southeastern Sweden	–	–	–	–	–	–
8. Uppsala, Sweden	24:16	12:24	50:50	–	2:3	7:4
9. Northern Sweden	–	–	–	–	–	–
10. Norway, NHSS	–	–	–	–	–	–
11. Tromsö, Norway	13:31	24:12	39:50		3:1	6:3
Europe – South						
12. Northern Italy	9:15	8:10	46:46	8:10	–	–
13. Vaud, Switzerland	18:24	24:30	48:52	12:9	–	–
14. Athens, Greece	–	–	–	–	–	–
Total	17:22	24:24	45:46	6:7	3:2	26:24

[a] Never users excluded.
[b] Months.
[c] Years.
[d] Parous women only.

use somewhat younger in North America, Northern Europe and Switzerland compared with Asia. No appreciable difference in time since stopping use was evident.

Overall, 808 (38%) cases versus 1290 (39%) controls had ever used OCs (OR of 1.2; 95% CI 1.0 to 1.4) (Table 2). The OR for ever use was 1.21 (95% CI 0.9 to 1.6) for studies including prevalent cases diagnosed before 1980, 1.13 (95% CI 0.8 to 1.5) for those diagnosed between 1981 and 1985, and 1.12 (95% CI 0.9 to 1.5) for those diagnosed after 1985. There was no relation with duration of use, with age at first use, or with OC use before first birth. However, the OR was significantly above unity for current OC users (91 cases, 118 controls, OR = 1.5, 95% CI 1.0 to 2.1), and declined with increasing time since last use to 1.1 for 1 to 5 years, 1.2 for 6 to 10 years, and to 1.1 for more than 10 years since last use.

In Figure 1, ORs and CIs for ever OC users in various studies were plotted: in 4 studies the OR was below unity, in eight above unity, and in one exactly 1.0. Only in one study was the estimate significantly different from the overall pooled estimate of 1.2. Corresponding values for current users are shown in Figure 2. Six out of the 7 studies providing this information had ORs above unity.

Similar analyses were conducted for papillary and follicular thyroid cancers separately. The association was stronger for papillary cancers, with ORs of 1.2 (95% CI 1.0 to 1.4) for ever users and of 1.6 (95% CI 1.1 to 2.4) for current users. No apparent relation was observed for follicular malignancies (OR = 1.0; 95% CI 0.7 to 1.4 for ever users; OR = 0.7, 95% CI 0.2 to 1.8, for current users).

When selected measures of OC use were considered in separate strata of geographic area, no significant differences were observed (Table 3). The ORs for ever use and duration of use tended to decrease with increasing age at diagnosis, possibly reflecting an effect of recency of use (Table 3). This pattern was also observed for papillary carcinomas as a separate group.

Descriptive data on HRT use are given in Table 4. To favour comparability across populations for descriptive purpose, prevalence of HRT use is given in postmenopausal women only. The prevalence and the duration of use were somewhat higher in North America, although any inference from these data should consider the different age distribution of cases and controls of

Table 5. Distribution[a] of thyroid cancer cases and controls according to selected indicators of hormone replacement therapy (HRT) and other female hormone use, and corresponding odds ratio (OR)[b]

Variable	Cases	Controls	OR (95% CI)[c]
HRT use[d]			
Never	1195 (92)[e]	2095 (91)	1[f]
Ever	110 (8)	205 (9)	0.8 (0.6–1.1)
χ^2 heterogeneity across studies 18.13; 7df ($p = 0.01$)			
Duration of HRT use[d] (months)			
Never	1017 (91)	1712 (91)	1[f]
< 24	50 (4)	86 (4)	0.7 (0.4–1.1)
≥ 24	49 (4)	91 (5)	0.9 (0.6–1.3)
χ^2 heterogeneity across studies 11.89; 6df ($p = 0.06$)			
per 24 months			1.0 (0.9–1.0)
χ^2 heterogeneity across studies 8.55; 6df ($p = 0.20$)			
Age at starting HRT use[d] (years)			
Never users	1195 (92)	2095 (91)	1[f]
< 50	89 (7)	132 (6)	1.0 (0.7–1.3)
≥ 50	19 (1)	65 (3)	0.5 (0.3–0.9)
χ^2 heterogeneity across studies 10.94; 7df ($p = 0.14$)			
per 5 years			
χ^2 heterogeneity across studies 8.32; 7df ($p = 0.31$)			0.8 (0.7–1.0)
Time since last HRT use[d] (years)			
Never	1021 (92)	1788 (93)	1[f]
< 5	32 (3)	44 (2)	0.9 (0.5–1.5)
≥ 5	54 (5)	93 (5)	0.9 (0.6–1.3)
χ^2 heterogeneity across studies 6.54; 5df ($p = 0.26$)			
per 5 years			1.1 (0.9–1.4)
χ^2 heterogeneity across studies 3.90; 5df ($p = 0.56$)			
Infertility treatment[g]			
Never	708 (97)	1138 (98)	1[f]
Ever	22 (3)	29 (2)	1.6 (0.9–2.9)
χ^2 heterogeneity across studies 7.44; 4df ($p = 0.11$)			
Lactation suppression[h] (parous women only)			
Never	505 (74)	774 (76)	1[f]
Ever	178 (26)	242 (24)	1.5 (1.1–2.1)
χ^2 heterogeneity across studies 1.57; 5df ($p = 0.90$)			

[a] Based on studies 1–4, 8, 11–13 for ever HRT use; 1, 3–4, 8, 11–13 for duration, 1–4, 8, 11–13 age at starting; 1–4, 12–13 for time since stopping; 1, 3, 4, 8, 11 for infertility treatment; 1, 2, 4, 5, 8, 11 for lactation suppression.
[b] Estimates from conditional logistic regression conditioned on center and age, and adjusted for history of radiation and age.
[c] 95% confidence interval.
[d] Adjusted also for menopausal status and type of menopause.
[e] The percentage is given in parentheses.
[f] Reference category.
[g] Adjusted also for parity.
[h] Adjusted also for parity and breastfeeding.

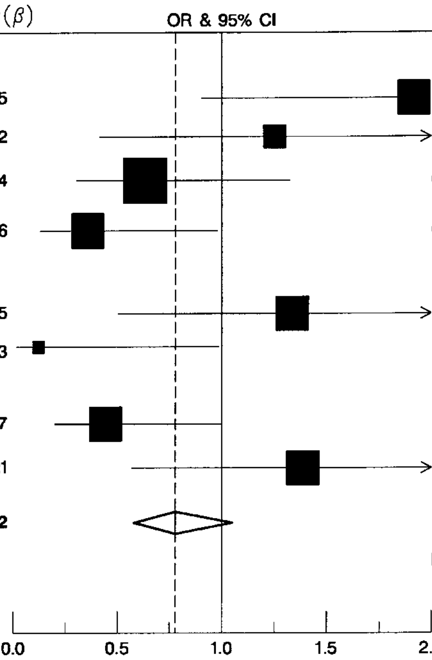
various studies. Overall, 110 (8%) cases and 205 (9%) controls had ever used HRT (OR = 0.8; 95% CI 0.6–1.1) (Table 5). No pattern of risk was apparent for duration or time since last HRT use, but the OR was below unity for women who had started HRT use at age 50 or over (OR = 0.5, 95% CI 0.3 to 0.9).

The plots of ORs and CIs for ever HRT use in various studies are shown in Figure 3. In 4 studies the OR was above unity, and in 4 below unity, and the test for heterogeneity was significant. No heterogeneity was observed with geographic area, whereas the ORs for HRT ever use, duration and age at first use were higher at younger age, and tended to decrease with increasing age at diagnosis (Table 6).

Use of fertility drugs was reported by 22 (3%) cases and 29 (2%) controls, yielding to an overall OR of 1.6 (95% CI 0.9 to 2.9) (Table 5). Treatment for lactation suppression was reported by 178 (26%) parous cases and 242 (29%) controls: the corresponding OR was 1.5 (95% CI 1.1–2.1) (Table 5). The association with lactation suppression was stronger at younger age at diagnosis (Table 6).

STUDY*	EVER Cases/Controls	NEVER Cases/Controls	STATISTICS β	var(β)	ODDS RATIO** OR ± SD
AMERICA – USA					
292 Los Angeles	43/32	249/260	0.65	0.15	1.9 ± 0.7
185 Western Washington	7/9	178/383	0.22	0.32	1.3 ± 0.7
140 Hawaii	16/48	124/280	−0.46	0.14	0.6 ± 0.2
109 Connecticut	9/26	99/181	−1.02	0.26	0.4 ± 0.2
EUROPE – NORTH					
133 Uppsala – Sweden	12/12	121/189	0.29	0.25	1.3 ± 0.7
58 Tromsø – Norway	3/15	53/120	−2.09	1.13	0.1 ± 0.1
EUROPE – SOUTH					
291 Italy	10/28	281/399	−0.81	0.17	0.5 ± 0.2
100 Switzerland	10/35	90/283	0.33	0.21	1.4 ± 0.6
Total:	**110/205**	**1195/2095**	**−0.24**	**0.02**	**0.8 ± 0.1**

Test for heterogeneity between studies: χ^2 (7 d.f.) = 18.13; P = 0.01 P = 0.0981



*Studies in each group sorted by number of cases
**Relative to never users
Adjusted for study, age, history of radiation, menopausal status and type of menopause

Fig. 3. Odds ratio of thyroid cancer in ever versus never users of hormone replacement therapy.

Discussion

This pooled analysis of 13 studies provides data on female hormone use, based on over 2,100 women with thyroid cancer and over 3,300 controls, of whom almost 40% had ever used OCs. These data provide reassuring evidence of the absence of an association between OC use and thyroid cancer risk. The pooled OR for ever use was 1.2, and there was no duration–risk relationship, nor any relationship with age at first use, or use before first birth. The OR was significantly above unity for current users, but tended to decline with increasing time since stopping. The OR was 1.1 ten years after stopping, and there was no evidence of association with past use.

This moderate excess thyroid cancer risk in current OC users may be partly due to diagnostic or ascertainment bias, *e.g.*, increased surveillance for thyroid masses among OC users. A large proportion of thyroid carcinomas in young women are detected in the absence of symptoms or signs during clinical examinations for other reasons [1]. Alternatively, these findings may reflect a real association restricted to current or recent users. This pattern of risk is similar to that described for breast cancer, where the relation with OCs is restricted to current or recent users [17, 18]. This suggests a role in one of the latest stages of the process of carcinogenesis, *i.e.*, promotion rather than initiation [19].

Our finding is strengthened by the consistency of the results across studies, in spite of the differences in study methods, in the populations examined, and their variable patterns of OC use. Thus, it is likely that the few apparent inconsistencies in published reports are partly or largely attributable to chance. By pooling data from many studies, we found moderate excess risk among current or recent OC users, but did not observe a substantial excess risk after stopping use. With this analysis, the epidemiological and public health implications of the relationship between current OC use and thyroid cancer have been clarified.

In our analysis of 8 studies providing data on HRT on more than 1,300 cases and 2,300 controls, the pooled estimate was below unity. The only significantly reduced OR, however, was for women who had started use above age 50. This may result from some selection bias, since women with thyroid disorders may be selectively excluded from HRT. Whatever the real underlying factors, these data indicate that HRT use does not lead to increased risk of thyroid cancer.

Table 6. Odds ratios[a] of thyroid cancer according to selected indicators of hormone replacement therapy (HRT) and other female hormone use in strata of geographical area and age at diagnosis

Variable	Geographical area				Age at diagnosis		
	USA	ASIA	North EU	South EU	≤ 35	35–55	≥ 56
HRT use[b,c]							
Ever use	0.9	–	0.6	0.7	1.9	0.9	0.5
χ^2 heterogeneity		0.4; 2df ($p = 0.81$)				7.5; 2df ($p = 0.02$)	
Duration of HRT use[b]							
per 24 months	1.0	–	0.9	0.9	1.5	1.0	0.9
χ^2 heterogeneity		0.3; 2df ($p = 0.86$)				4.9; 2df ($p = 0.09$)	
Age at starting HRT use[b]							
per 5 year increase	0.8	–	1.4	0.9	1.3	1.0	0.9
χ^2 heterogeneity		1.1; 2df ($p = 0.59$)				3.8; 2df ($p = 0.15$)	
Time since last HRT use[b]							
per 5 year increase	1.1	–	–	1.3	0.3	1.2	1.4
χ^2 heterogeneity		0.0; 1df ($p = 0.84$)				2.0; 2df ($p = 0.37$)	
Infertility treatment[d]							
Ever use	1.9	–	1.0	–	1.0	2.7	5.4
χ^2 heterogeneity		0.9; 1df ($p = 0.34$)				3.8; 2df ($p = 0.15$)	
Lactation suppression[c,e] (parous women only)							
Ever use	1.3	2.5	1.6	–	2.3	1.7	0.7
χ^2 heterogeneity		0.0; 2df ($p = 100$)				6.3; 2df ($p = 0.04$)	

[a] Estimates from conditional logistic regression conditioned on center and age, and adjusted for history of radiation and age.
[b] Adjusted also for menopausal status and type of menopause.
[c] Reference category: never users.
[d] Adjusted also for parity.
[e] Adjusted also for parity and breastfeeding.

A modest, nonsignificant excess risk was observed for women who had used fertility treatment, and a moderate, but significant, excess risk was seen for women who reported use of lactation suppression treatment. History of infertility was moderately related to the risk of thyroid cancer [8, 9], and is, therefore, difficult to understand whether the association, if any, is due to the treatment or to other correlates of infertility itself.

Despite substantial variation by geographic area in the proportion of women reporting use of lactation suppression, elevated ORs were found in all studies. It seems likely that more accurate recall of these treatments by cases at least partly explains their apparent association with thyroid cancer, since it is difficult to explain on a biological basis how such short-term treatment can appreciably influence subsequent thyroid cancer risk.

In conclusion, this collaborative re-analysis of available individual data on exogenous female hormones and thyroid cancer provides evidence of an absence of persistent excess risk of thyroid carcinoma following use of OCs and HRT, although current OC users may have a moderately elevated thyroid cancer risk. The association with current OC use may reflect tumor promotion, or diagnostic and ascertainment bias. However, the decline in risk stopping OC use has important and reassuring implications for individual and public health risk.

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